A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12 Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy

NCT04250207

Clinical Study Protocol Ver.: 1.0

Document Date: 16 August 2019

CLINICAL STUDY PROTOCOL
EudraCT Number 2019-003280-22
A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12-Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy

PROTOCOL K-321-201

Sponsor:	Kowa Research Institute, Inc. 430 Davis Drive, Suite 200 Morrisville, NC 27560
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	1.0 (Original)
Date of Protocol:	16 August 2019

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Integrated Addendum to E6 (R1): Guideline For Good Clinical Practice E6 (R2), the principles of the Declaration of Helsinki, and applicable regulations in the countries where the study will be conducted.

Protocol Approval – Sponsor Signatories

Study Title A double-masked, randomised, placebo-controlled, parallel-group, 12-week, Phase 2 study to investigate the safety and efficacy of ripasudil (K-321) eye drops after descemetorhexis in patients with Fuchs endothelial corneal dystrophy

Protocol Number K-321-201

Protocol Date 16 August 2019

Protocol accepted and approved by:

[redacted]
Kowa Research Institute
[redacted]

[redacted]
Kowa Research Institute
[redacted]

[redacted]
Kowa Research Institute
[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A double-masked, randomised, placebo-controlled, parallel-group, 12-week, Phase 2 study to investigate the safety and efficacy of ripasudil (K-321) eye drops after descemetorhexis in patients with Fuchs endothelial corneal dystrophy" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 1.0, dated 16 August 2019, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Integrated Addendum to E6 (R1): Guideline For Good Clinical Practice E6 (R2), the principles of the Declaration of Helsinki, and applicable regulations in the countries where the study will be conducted. I will not make changes to the protocol before consulting with Kowa Research Institute, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorised to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorisation from Kowa Research Institute, Inc.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:

K-321-201

Title:

A Double-Masked, Randomised, Placebo-Controlled, Parallel-Group, 12-Week, Phase 2 Study to Investigate the Safety and Efficacy of Ripasudil (K-321) Eye Drops After Descemetorhexis in Patients with Fuchs Endothelial Corneal Dystrophy

Sponsor:

Kowa Research Institute, Inc.
430 Davis Drive, Suite 200
Morrisville, NC 27560

Study Phase:

Phase 2

Study Sites:

Approximately 30 sites in the United States, Europe, and Australia

Indication:

The treatment of Fuchs endothelial corneal dystrophy after descemetorhexis

Rationale:

In Fuchs endothelial corneal dystrophy (FECD), there is an increased rate of loss of endothelial cells, starting in the centre of Descemet's membrane and spreading to the periphery. There is an increased deposition of extracellular matrix on Descemet's membrane, resulting in excrescences known as guttae, which are a marker of the condition. Guttae may coalesce and inhibit the migration of endothelial cells. Eventually the corneal endothelium ceases to function effectively, and the cornea begins to cloud, leading eventually to blindness.

Currently, most patients undergoing keratoplasty for FECD have Stage 2 disease and the procedure starts with descemetorhexis, removing an area of the roughened and irregular Descemet's membrane (including the central guttae) from the diseased cornea. The excised area is replaced with a graft of endothelial cells: either donor Descemet's membrane with a thin layer of corneal stroma (Descemet stripping endothelial keratoplasty [DSEK]), or, increasingly commonly, donor Descemet's membrane alone (Descemet's membrane endothelial keratoplasty [DMEK]).

Experience with failed grafts has indicated that even though there is an underlying abnormality of endothelial cells in FECD, areas of stroma exposed by descemetorhexis can be re-endothelialised and the migrated endothelial cells can maintain corneal transparency. Mathematical modelling of the healing of an inadvertent [redacted] diameter descemetorhexis in an elderly man without FECD suggested that normal healing is achieved by a redistribution of peripheral endothelial cells into the central defect without any increase in the number of endothelial cells. This led to the proposal that some cases

of FECD, particularly those with relatively preserved peripheral endothelial cells, can be treated by descemetorhexis alone.

There is a medical need for medication that can speed healing after descemetorhexis and that can help establish a high, functional endothelial cell density (ECD) to maintain corneal transparency.

Ripasudil ophthalmic solution 0.4% (K-321) is a Rho-associated protein kinase (ROCK) inhibitor that has been marketed in Japan since December 2014 as Glanatec®, with twice daily dosing for glaucoma and ocular hypertension. Studies in endothelial cells have indicated that K-321 can lead to reduction of apoptosis, enhancement of cell proliferation, and increased rates of migration, all of which may support endothelial healing. Macsai et al in 2019 reported results from a small study of 18 patients with FECD and central confluent guttae of up to 5 mm diameter who underwent Descemet stripping only (DSO) and were subsequently treated with either ripasudil ophthalmic solution 0.4% four times daily or no ripasudil for 2 months. Overall, patients who underwent DSO with ripasudil recovered vision more quickly [redacted]. The patients in the no-ripasudil group had a [redacted] while in the ripasudil group there was [redacted] In the short-term studies (8 weeks duration and less) for the development of Glanatec, there were no [redacted] (Kowa Company Ltd 2019).

Kowa proposes to pursue development of K-321 (ripasudil ophthalmic solution) for the following indication: "the treatment of Fuchs corneal dystrophy after descemetorhexis." This will be the first Kowa-sponsored study in patients for this indication.

Objectives:

Primary Objective:

The primary objective of this study is to investigate the effect of K-321 dosed for 12 weeks on central ECD in patients with FECD after descemetorhexis.

Secondary Objectives:

The secondary objectives of this study are the following:

- to investigate the effect of K-321 on central ECD, corneal thickness, and corneal clarity in patients with FECD at each visit after descemetorhexis out to 52 weeks
- to assess the safety and tolerability of K-321 in patients with FECD at each visit after descemetorhexis out to 52 weeks

Exploratory Objectives:

[redacted]

[redacted]

Study Design:

This is a multi-centre, double-masked, randomised, parallel-group, placebo-controlled, 2-period study of patients with FECD after descemetorhexis.

The first period is the treatment period, consisting of a screening visit within a 1- to 4-week screening period, a descemetorhexis and randomisation visit, a 12-week full treatment period containing 7 interim visits (including 1 optional visit at Week 2) and an end-of-treatment (EOT) visit scheduled for Week 12. During the 2 weeks immediately following the EOT visit, each enrolled patient will taper dosing of study drug to zero.

The second period is a follow-up observation period of 40 weeks, including the tapering phase and containing 4 interim visits and an end-of-study (EOS) visit. Patients are not to self-administer study drug after approximately Week 14. Patients will be considered to have completed the study with the completion of their EOS visit (scheduled for Week 52).

There are 3 treatment groups: K-321 ophthalmic solution 0.4% dosed 4 times daily (QID); K-321 ophthalmic solution 0.4% dosed 2 twice daily (BID); and placebo.

After obtaining informed consent at Visit 1, the investigator will select one eye as the study eye and the patient will come back for the descemetorhexis operation and random assignment to treatment after 1 to 4 weeks (Visit 2). At Visit 2, each patient's eligibility for study participation will be confirmed, including a successful descemetorhexis operation that meets the inclusion criteria.

After eligibility is confirmed, patients will be randomly assigned to the 3 treatment groups (in a 1:1:1 ratio). All patients will be instructed to apply the study drug only to the study eye.

Except on days of study visits on Day 1 through Week 12 (not including Visit 9) during the treatment period, study drug will be dosed by the patient 4 times per day: morning, mid-day, evening, and night. Each patient will be provided with 2 sets of colour-coded [redacted] one set to be applied morning and night (M/N) and the other to be applied mid-day and evening (MD/E).

On study visit days Visit 3 through Visit 9, patients will not apply any study drug until after all study measurements have been completed; thereafter on those days, patients will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day. Additionally, on Visit 3 they must first apply study drug within [redacted] after the end of the descemetorhexis procedure on Day –1 (Visit 2).

At Visit 9 (Week 12), patients will enter the drug-tapering phase of the follow-up period, and new study drug will be dispensed without M/N or MD/E colour coding. All patients will self-administer their tapering-phase study drug BID (morning and night) for a week, then once daily in the morning for a week, and then will discontinue study drug.

During the follow-up period, patients will attend 5 study visits, starting at Week 16 (Visit 10).

[redacted] will determine central ECD by analysing digital images of the corneal endothelium.

Keratoplasty may be offered as a rescue surgical procedure to an enrolled patient if the investigator judges that endothelial healing is not complete at Visit 9 (Week 12), or earlier if the investigator considers that the patient needs urgent treatment.

Study Population:

Inclusion Criteria:

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is at least 18 years old at the screening visit (Visit 1).
2. Has a diagnosis of FECD at Visit 1.
3. Has confluent central guttae in the study eye that can be removed by descemetorhexis of a circular area of [redacted] diameter or less (at Visit 1).
4. Has a study eye with best corrected visual acuity (BCVA) of 75 letters or fewer by Early Treatment Diabetic Retinopathy Study (ETDRS) testing (Snellen equivalent of 20/32 or worse) at Visit 1.
5. The study eye descemetorhexis at Visit 2 is confirmed to have excised a central area with confluent guttae and a diameter of [redacted] Guidance for performing the study eye descemetorhexis and measurement of the excised area will be provided in the study manual.
6. Can understand the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements before any study-specific assessment is performed.

Exclusion Criteria:

Patients meeting any of the following criteria will be excluded from the study:

1. Is a female patient and any of the following is true:

    - is pregnant or lactating/breastfeeding, or
    - is not surgically sterile, not post-menopausal (no menses for the previous 12 months), or not practising an effective method of birth control as determined by the investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or partner with vasectomy).

If a patient is female and of childbearing potential, she must have a negative urine pregnancy test result at Visit 2 before the descemetorhexis. Women of childbearing potential must also agree to use effective contraception throughout the study.

A female of childbearing potential is defined as a woman who has experienced menarche and has not undergone successful surgical sterilisation or is not post-menopausal, and a

post-menopausal woman is defined as having had no menses for the previous 12 months (without a known cause).

2. Has a study eye with confluent guttae in the periphery or confluent guttae outside the stripped area (individual guttae are allowed).
   Note that patients may have individual or small number of guttae remaining outside the stripped area, but there should be no areas of confluent guttae remaining after the descemetorhexis. For example, a patient who had 5 to 10 guttae remaining in a few spots around the circumference of the descemetorhexis would not be excluded by this criterion.
3. Has a study eye with a history of cataract surgery within 90 days of Visit 1.
4. Has a study eye with a history of any previous ocular surgery other than for cataract.
5. Has a non-study eye with a history of any previous ocular surgery within 30 days of Visit 1.
6. Plans to receive any surgical treatment on the study eye during any study period, other than the study descemetorhexis.
7. Plans to receive any surgical treatment for FECD or cataract on the non-study eye in the screening or treatment period.
8. Has advanced corneal stromal oedema defined as the presence of widespread haze or bullae on slit-lamp examination.
9. Has a study eye with central corneal thickness ≥ 670 μm.
10. Has known severe comorbidities that may interfere with descemetorhexis (eg, a bacterial, viral, or fungal ophthalmic infection).
11. Has any clinically significant ocular condition other than FECD or cataract that requires medication or ocular surgery.
12. Has diabetes with poor blood sugar control (eg, HbA1c value > 8.5%).
13. Has used contact lenses within 7 days of Visit 1.
14. Has hypersensitivity to any ophthalmic medication used for diagnosis or treatment, including eye drops containing antibiotic(s) or glucocorticoid(s).
15. Has known hypersensitivity to any component of the study drugs.
16. Has previously used ripasudil, netarsudil, or other ROCK inhibitors.
17. Has used any investigational medications within 30 days of Visit 1.
18. Has a positive urine test result for drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or alcohol at screening.
19. Has donated more than 450 mL of blood within 60 days of Visit 1.
20. Is a member or a family member of the professional or ancillary personnel working at the study site or the sponsor involved in the study.
21. Has a concomitant medical or psychological condition that could interfere with study participation or is otherwise not suitable for entry into the study in the opinion of the investigator.

Estimated Study Duration: The maximum total study period for each enrolled patient is 56 weeks, with a maximum of 15 visits (including 1 optional visit at Week 2).

Efficacy Assessments:

Efficacy assessments include corneal ECD, corneal thickness, corneal oedema, corneal morphology, BCVA, contrast sensitivity, and the [redacted]

Safety Assessments:

Safety assessments include the identification of AEs; ocular safety assessments of both eyes (including: slit-lamp examination without pupil dilation to evaluate the condition of the lids, conjunctiva, anterior chamber, and cornea; intra-ocular pressure measurement; and ocular examination with pupil dilation using an indirect ophthalmoscope according to the current standard of practice to evaluate the condition of the vitreous, macula, retina, optic nerve, choroid, and retinal periphery); vital sign measurements; and laboratory examinations.

Study Drug, Dosage, and Route of Administration:

Study drug is either K-321 ophthalmic solution containing ripasudil 0.4% (K-321 0.4%) or matching placebo. The K-321 treatments will comprise either BID or QID dosing of K-321, as presented in Table 1.

Table 1 Dosing Regimen for Each Treatment Group From Day 1 to Visit 9

Treatment	Morning	Mid-day	Evening	Night
K-321 QID	K-321 0.4%	K-321 0.4%	K-321 0.4%	K-321 0.4%
K-321 BID	K-321 0.4%	Placebo	Placebo	K-321 0.4%
Placebo	Placebo	Placebo	Placebo	Placebo

For each dose, patients must instil 1 drop to the study eye only and then close the eyelids, pressing on the lacrimal punctum. Patients will be advised to keep the eye closed for 1 to 5 minutes before opening the eye. Any other concurrent ocular medication(s) may be applied at least 5 minutes following instillation of study drug.

Sample Size:

Approximately 60 patients will be enrolled in the study. A sample size of 20 patients in each group will be needed to detect a difference of [redacted] in the measurement in the corneal ECD at Week 12 between K-321 0.4% QID/BID and placebo groups with a power of [redacted] for Step 1 and a power of [redacted] for Step 2 using a Wilcoxon rank sum test with a 0.050 two-sided significance level with closed testing procedures. Sample size was calculated by simulation. For the simulation, based on the existing literature, placebo was assumed to be distributed normally with a [redacted] and K-321 was assumed to be distributed normally with a [redacted]. Proportion of unmeasurable value of Week 12 due to corneal oedema and proportion of [redacted] value of Week 12 due to the withdrawal were assumed to be about 10% and about 5%, respectively.

Statistical Methods:

Continuous variables will be summarised using the mean, the SD, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages.

All statistical tests will be 2-sided and performed using a 0.05 significance level, leading to 95% (2-sided) CIs.

A closed 2-step ordered testing procedure will be used to control overall type I error for the primary efficacy endpoint, central corneal ECD at Week 12. In step 1, the K-321 0.4% QID group will be statistically compared with the placebo group. If the step 1 comparison is significant, step 2 will be performed to statistically compare K-321 0.4% BID group with the placebo group. If the statistical comparison made during step 1 is not significant, testing will still be performed to compare the BID group to placebo; however, all p values will be considered nominal/descriptive only.

No other measures will be taken to control error for the multiple secondary and exploratory endpoints or multiple treatment comparisons.

The primary analysis of central corneal ECD will be performed on the study eye within the full-analysis set (FAS) via a Wilcoxon rank sum test and will be based on assessments performed by specular microscopy. Testing will be performed in a pairwise manner with each dosing regimen (QID and BID) of K-321 0.4% compared to placebo.

Secondary endpoints will be summarised for the FAS. Endpoints based on continuous measures (central ECD at each visit, central corneal thickness change from baseline to each visit, and percent change of central corneal thickness from baseline to each visit) will be analysed by pairwise Wilcoxon rank sum tests comparing each active K-321 0.4% treatment regimen to placebo.

Endpoints based on the number and percentage of patients achieving the endpoint (patients who achieve central ECD of 700 cells/mm^2 or more, patients who achieve cornea clearance at each visit, patients who achieve a cornea thickness less than or equal to baseline cornea thickness at each visit, and patients who have no corneal oedema at each visit) will be analysed by pairwise Fisher's Exact or Pearson chi-square tests comparing each active K-321 0.4% treatment regimen to placebo. The 95% CI for the difference in percentage of patients achieving the endpoint will also be presented.

Endpoints based on time-to-event endpoints (time to achieve central ECD 700 cells/mm2 or more, time to cornea clearance, time to return of cornea thickness to less than or equal to baseline cornea thickness, time to no corneal oedema) will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo. Kaplan-Meier estimates and plots will also be presented. Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be [redacted] Patients who receive rescue keratoplasty will be [redacted]

Safety parameters include monitoring of AEs, TEAEs, vital sign measurements, laboratory examinations, slit-lamp biomicroscopy, IOP, and ophthalmoscopy. Safety data

will be summarised and listed with no statistical hypothesis testing performed. Continuous variables will be summarised using the mean, the SD, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages.

Version and Date of Protocol:

Version 1.0 (Original), 16 August 2019

List of Abbreviations

Abbreviation	Definition
AE	adverse event
BCVA	best controlled visual acuity
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
CRO	contract research organisation
CS	clinically significant
CV	curriculum vitae
DMEK	Descemet membrane endothelial keratoplasty
DSEK	Descemet stripping endothelial keratoplasty
DSO	Descemet stripping only
ECD	endothelial cell density
eCRF	electronic case report form
EDC	electronic data capture
EOS	end-of-study
EOT	end-of-treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full-analysis set
FDA	US Food and Drug Administration
FECD	Fuchs endothelial corneal dystrophy
GCP	Good Clinical Practice
HbA1c	haemoglobin A1c (glycated haemoglobin)
HRT	Heidelberg retina tomography
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IOP	intra-ocular pressure
IRB	institutional review board
IWRS	interactive web response system
LOCF	last-observation-carried-forward

Abbreviation	Definition
M/N	morning and night
MD/E	mid-day and evening
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NCS	not clinically significant
PPS	per-protocol set
QID	4 times daily
ROCK	Rho-associated protein kinase
SAE	serious adverse event
SAP	statistical analysis plan
SFS	safety set
SOA	schedule of study site activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
[redacted]	[redacted]

List of Terms

Term	Definition
Descemetorhexis	Removal of an area of roughened and irregular Descemet membrane along with central guttae (also referred to herein as Descemet membrane stripping)

1 Introduction

In the early 20th century, Ernst Fuchs described a bilateral corneal dystrophy now referred to as Fuchs endothelial corneal dystrophy (FECD). The primary defect in FECD seems to be related to the endothelial cells that normally sit on a modified basement membrane (Descemet's membrane) that lines the inner surface of the cornea.

In the normal adult human cornea, the endothelial cell density (ECD) on Descemet's membrane is in the range of 2,000 to 3,500 cells/mm^2 (Ianchulev et al 2019) and the endothelial cells maintain the cornea in a state of relative dehydration, which preserves corneal transparency. During adulthood there is continuous loss of endothelial cells at an approximate rate of 0.6% per year. Since the number of endothelial cells cannot increase because of a state of mitotic arrest, gaps caused by apoptosis are filled by the migration of adjacent cells that increase in size and change shape. The function of the corneal endothelium can be maintained while the ECD is maintained above approximately 400 cells/mm^2. Below that threshold (due to disease, trauma or old age), there is decompensation of the endothelial pumping mechanism and corneal oedema produces a visual haze (Van den Bogerd et al 2018).

In FECD, there is an increased rate of loss of endothelial cells, starting in the centre of Descemet's membrane and spreading to the periphery. There is an increased deposition of extracellular matrix on Descemet's membrane, resulting in excrescences known as guttae, which are a marker of the condition. Guttae may coalesce and inhibit the migration of endothelial cells. Eventually the corneal endothelium ceases to function effectively, and the cornea begins to cloud, eventually leading to blindness (Elhalis et al. 2010).

There are clinical staging systems for FECD that describe the progression of the disease (Elhalis et al. 2010). Stage 1 is characterised by the presence of corneal guttae that are centrally located, non-confluent, and asymptomatic. Guttae may also form in response to trauma, toxins, or infection and may not be indicative of FECD. Guttae appearing with age are considered a normal finding in the elderly if they appear in the periphery. In Stage 2, central guttae start to coalesce and spread to the periphery and there is loss of endothelial cells, with ECD being inversely proportional to the number of guttae. The cells become much more variable in size and lose their regular shape (pleomorphism), and painless visual symptoms start to appear. The irregularity of the Descemet's membrane, and particularly the presence of central confluent guttae, may lead to forward scatter of light in the eye, loss of

visual contrast sensitivity, and impairment of visual acuity, even in the absence of oedema (Watanabe et al 2015). In the early stages of the disease, oedema of the stroma causes blurriness of vision in the morning that clears during the day, but this progresses to permanent loss of visual acuity with glare. In Stage 3, there is more marked corneal oedema and painful sub-epithelial and epithelial bullae may form. Rupture of the bullae disrupts the outer surface of the cornea and exposes the patient to risk of infection. Finally, in Stage 4, the cornea becomes opaque and new vessel growth may occur. In addition, there may be sub-epithelial fibrous tissue formed due to long-standing oedema. In this stage, the eye becomes blind, but the pain may subside (Elhalis et al. 2010).

Fuchs endothelial corneal dystrophy is currently treated by a variety of keratoplasty techniques, including full-thickness cornea transplantation (for Stages 3 and 4) and 2 techniques involving transplantation of a graft of donor endothelial cells on donor Descemet's membrane. Currently, most patients undergoing keratoplasty for FECD have Stage 2 disease and the procedure starts with descemetorhexis, removing an area of the roughened and irregular Descemet's membrane (including the central guttae) from the diseased cornea. The excised area is replaced with a graft of endothelial cells: either donor Descemet's membrane with a thin layer of corneal stroma (Descemet stripping endothelial keratoplasty [DSEK]), or, increasingly commonly, donor Descemet's membrane alone (Descemet's membrane endothelial keratoplasty [DMEK]).

Experience with failed grafts has indicated that even though there is an underlying abnormality of endothelial cells in FECD, areas of stroma exposed by descemetorhexis can be re-endothelialised and the migrated endothelial cells can maintain corneal transparency. Mathematical modelling of the healing of an inadvertent 5-mm diameter descemetorhexis in an elderly man without FECD suggested that normal healing is achieved by redistribution of peripheral endothelial cells into the central defect without any increase in the number of endothelial cells (Jullienne et al 2015). This led to the proposal that some cases of FECD, particularly those with relatively preserved peripheral endothelial cells, can be treated by descemetorhexis alone (Garcerant et al 2019).

There are limits to the ability of the endothelium to heal. In a recent analysis of cases of patients who underwent descemetorhexis without grafting as a possible treatment for FECD (compiled from multiple papers), 31 (65%) out of 47 cases eventually achieved a clear cornea, with healing taking place as early as 1 month after the procedure (Van den Bogerd et

al 2018). If there was persistent oedema at 6 months, then it was unlikely to resolve. If corneal oedema did not clear, some patients' corneas cleared without residual stromal damage after DMEK performed as rescue therapy between 4 and 8.5 months after Descemet's membrane stripping (Van den Bogerd et al 2018). All keratoplasty procedures, including DMEK, are associated with risks of graft detachment, graft failure or immune rejection. There is a medical need for medication that can speed healing after descemetorhexis and that can help establish a high, functional ECD to maintain corneal transparency.

Ripasudil ophthalmic solution 0.4% (K-321) is a Rho-associated protein kinase (ROCK) inhibitor that has been marketed in Japan since December 2014 as Glanatec®, with twice daily (BID) dosing for glaucoma and ocular hypertension. Studies in endothelial cells have indicated that K-321 can lead to reduction of apoptosis, enhancement of cell proliferation, and increased rates of migration, all of which may support endothelial healing (Kowa Company Ltd 2019). Moloney et al (2017) first reported use of a ROCK inhibitor to promote healing in patients with FECD treated with Descemet stripping only (DSO). More recently, Macsai et al (2019) reported results from a small study of 18 patients with FECD and central confluent guttae of up to [redacted] diameter who underwent DSO and were subsequently treated with either ripasudil ophthalmic solution 0.4% four times daily (QID) or no ripasudil for 2 months. Overall, patients who underwent DSO with ripasudil recovered vision more quickly [redacted] The patients in the no-ripasudil group had [redacted] while in the ripasudil group there was [redacted]. In the short-term studies (8 weeks duration and less) for the development of Glanatec, there were no [redacted] (Kowa Company Ltd 2019).

Kowa proposes to pursue development of K-321 (ripasudil ophthalmic solution) for the following indication: "the treatment of Fuchs endothelial corneal dystrophy after descemetorhexis." This will be the first Kowa-sponsored study in patients for this indication.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to investigate the effect of K-321 dosed for 12 weeks on central ECD in patients with FECD after descemetorhexis.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- to investigate the effect of K-321 on central ECD, corneal thickness, and corneal clarity in patients with FECD at each visit after descemetorhexis out to 52 weeks
- to assess the safety and tolerability of K-321 in patients with FECD at each visit after descemetorhexis out to 52 weeks

2.3 Exploratory Objectives

[redacted]

3 Investigational Plan

3.1 Study Design

This is a multi-centre, double-masked, randomised, parallel-group, placebo-controlled, 2-period study of patients with FECD after descemetorhexis. The study design is presented in Figure 3-1, and the schedule of study site activities (SOA) is presented in Table 6-1.

The first period is the treatment period, consisting of a screening visit within a 1- to 4-week screening period, a descemetorhexis and randomisation visit, a 12-week full treatment period containing 7 interim visits (including 1 optional visit at Week 2) and an end-of-treatment (EOT) visit scheduled for Week 12. During the 2 weeks immediately following the EOT visit, each enrolled patient will taper dosing of study drug to zero (Section 5.2).

The second period is a follow-up observation period of 40 weeks, including the tapering phase and containing 4 interim visits and an end-of-study (EOS) visit. Patients are not to self-administer study drug after approximately Week 14. The maximum total study period for each enrolled patient is 56 weeks, with a maximum of 15 visits (including the 1 optional visit). Patients will be considered to have completed the study with the completion of their EOS visit (scheduled for Week 52). The duration of the study is defined for each patient as the date signed written informed consent is provided through the last follow-up visit.

There are 3 treatment groups: K-321 ophthalmic solution 0.4% dosed QID, K-321 ophthalmic solution 0.4% dosed BID, and placebo. The procedures for randomly assigning study drug are presented in Section 5.1.

After obtaining informed consent at Visit 1, the investigator will select one eye as the study eye, and the patient will come back for the descemetorhexis operation and random assignment to treatment after 1 to 4 weeks (Visit 2). At Visit 2, each patient's eligibility for study participation will be confirmed, including a successful descemetorhexis operation that meets the inclusion criteria (Section 4.1). Guidance for the descemetorhexis will be provided in the study manual. Recommended post-descemetorhexis concomitant therapy is described in Section 5.8.1. Documentation of the descemetorhexis is discussed in Section 6.1.

After eligibility is confirmed, patients will be randomly assigned to the 3 treatment groups (in a 1:1:1 ratio). All patients will be instructed to apply the study drug only to the study eye.

Except on days of study visits on Day 1 through Week 12 (not including Visit 9) during the treatment period, study drug will be dosed by the patient QID (Section 5.2): morning (9 AM ±1 hour), mid-day (1 PM ±1 hour), evening (5 PM ±1 hour), and night (9 PM ±1 hour). Each patient will be provided with 2 sets of colour-coded [redacted] one set to be applied

morning and night (M/N) and the other to be applied mid-day and evening (MD/E). See Section 5.4.1 for a detailed description of packaging.

On study visit days Visit 3 through Visit 9, patients will not apply any study drug until after all study measurements have been completed; thereafter on those days, patients will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day. Additionally, on Visit 3 they must first apply the study drug within [redacted] after the end of the descemetorhexis procedure on Day –1 (Visit 2).

With the primary efficacy endpoint being assessed at Visit 9 (Week 12), if a patient applies any study drug on the day of Visit 9 before all study measurements have been completed, that patient's Visit 9 should be rescheduled within the visit window allowance (eg, the next day). For visits other than Visit 9 during the treatment period, a patient who applies study drug before all study measurements have been completed will be assessed as planned, and a protocol deviation must be recorded.

At Visit 9 (Week 12), patients will enter the drug-tapering phase of the follow-up period, and new study drug will be dispensed without M/N or MD/E colour coding (Section 5.2). All patients will self-administer their tapering-phase study drug BID (9 AM ±1 h and 9 PM ±1 h) for a week, then once daily (9 AM ±1 h) for a week, and then will discontinue study drug. At Visit 9, patients will apply the first dose of study drug [redacted] of completing study measurements and will apply the second dose at night, as scheduled.

During the follow-up period, patients will attend 5 study visits (Figure 3-1), starting at Week 16 (Visit 10).

Study activities and assessments will be performed at study visits as described in Table 6-1 and in Section 6. [redacted] will determine central ECD by analysing digital images of the corneal endothelium (Table 11-1).

Keratoplasty may be offered as a rescue surgical procedure to an enrolled patient if the investigator judges that endothelial healing is not complete at Visit 9 (Week 12), or earlier if the investigator considers that the patient needs urgent treatment (Section 5.8.2).

4 Patient Selection and Discontinuation/Withdrawal Criteria

4.1 Selection of Study Population

Approximately 60 patients will be enrolled at approximately 30 sites in the United States, Europe, and Australia. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Is at least 18 years old at the screening visit (Visit 1).
2. Has a diagnosis of FECD at Visit 1.
3. Has confluent central guttae in the study eye that can be removed by descemetorhexis of a circular area of [redacted] diameter or less (at Visit 1).
4. Has a study eye with best corrected visual acuity (BCVA) of 75 letters or fewer by Early Treatment Diabetic Retinopathy Study (ETDRS) testing (Snellen equivalent of 20/32 or worse) at Visit 1.
5. The study eye descemetorhexis at Visit 2 is confirmed to have excised a central area with confluent guttae and a diameter of [redacted] Guidance for performing the study eye descemetorhexis and measurement of the excised area will be provided in the study manual.
6. Can understand the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements before any study-specific assessment is performed.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Is a female patient and any of the following is true:

- is pregnant or lactating/breastfeeding, or
- is not surgically sterile, not post-menopausal (no menses for the previous 12 months), or not practising an effective method of birth control as determined by the investigator (eg, oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or partner with vasectomy).

If a patient is female and of childbearing potential, she must have a negative urine pregnancy test result at Visit 2 before the descemetorhexis. Women of childbearing potential must also agree to use effective contraception throughout the study.
A female of childbearing potential is defined as a woman who has experienced menarche and has not undergone successful surgical sterilisation or is not post-menopausal, and a post-menopausal woman is defined as having had no menses for the previous 12 months (without a known cause).

2. Has a study eye with confluent guttae in the periphery or confluent guttae outside the stripped area (individual guttae are allowed).
   Note that patients may have individual or small number of guttae remaining outside the stripped area, but there should be no areas of confluent guttae remaining after the descemetorhexis. For example, a patient who had 5 to 10 guttae remaining in a few spots around the circumference of the descemetorhexis would not be excluded by this criterion.
3. Has a study eye with a history of cataract surgery within 90 days of Visit 1.
4. Has a study eye with a history of any previous ocular surgery other than for cataract.
5. Has a non-study eye with a history of any previous ocular surgery within 30 days of Visit 1.
6. Plans to receive any surgical treatment on the study eye during any study period, other than the study descemetorhexis.
7. Plans to receive any surgical treatment for FECD or cataract on the non-study eye in the screening or treatment period.
8. Has advanced corneal stromal oedema defined as the presence of widespread haze or bullae on slit-lamp examination.

9. Has a study eye with central corneal thickness ≥ 670 µm.
10. Has known severe comorbidities that may interfere with descemetorhexis (eg, a bacterial, viral, or fungal ophthalmic infection).
11. Has any clinically significant ocular condition other than FECD or cataract that requires medication or ocular surgery (described in Section 5.8.3).
12. Has diabetes with poor blood sugar control (eg, HbA1c value > 8.5%).
13. Has used contact lenses within 7 days of Visit 1.
14. Has hypersensitivity to any ophthalmic medication used for diagnosis or treatment, including eye drops containing antibiotic(s) or glucocorticoid(s).
15. Has known hypersensitivity to any component of the study drugs.
16. Has previously used ripasudil, netarsudil, or other ROCK inhibitors.
17. Has used any investigational medications within 30 days of Visit 1.
18. Has a positive urine test result for drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or alcohol at screening.
19. Has donated more than 450 mL of blood within 60 days of Visit 1.
20. Is a member or a family member of the professional or ancillary personnel working at the study site or the sponsor involved in the study.
21. Has a concomitant medical or psychological condition that could interfere with study participation or is otherwise not suitable for entry into the study in the opinion of the investigator.

4.2 Discontinuation of Treatment and Withdrawal of Patients From the Study

The duration of the study is defined for each patient as the date signed written informed consent is provided through the date of the last study visit attended.

There are 3 scenarios that result in interruption of the treatment regimen. Interruption of treatment is defined as a temporary stopping of study drug treatment that resumes during the treatment period, due to an AE or any other reason. Early discontinuation of treatment is defined as permanent stopping of study drug treatment before completing Visit 9, scheduled

for Week 12. Investigators will strive to ensure that a patient who has interrupted treatment for a particular reason will not discontinue treatment unless discontinuation is medically imperative in the investigator's judgement. Early withdrawal from the study is defined as failing to complete Visit 14, scheduled for Week 52.

Study drug administration may be discontinued early at the discretion of the investigator (or designee) if the patient does not tolerate the dosing regimen or if, in the investigator's judgement, the patient's health may be jeopardised by continuing study treatment. Patients who discontinue treatment during the study will be encouraged by investigators to continue to participate in all scheduled study site visits and assessments, and study data will be collected for these patients per protocol. Every effort must be made to keep patients in the study (see Section 5.8.2 for a discussion of treatment discontinuation after rescue surgical procedures).

4.2.1 Reasons for Discontinuation or Withdrawal

Patients may discontinue treatment or withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort must be made to keep patients in the study. The reasons for patients discontinuing treatment or withdrawing early will be recorded.

A patient may discontinue treatment or be discontinued from treatment for any of the following reasons:

1. The patient does not meet the protocol inclusion or exclusion criteria.
2. The patient is non-compliant with the protocol.
3. The patient has a serious or intolerable AE that, in the investigator's opinion, requires withdrawal from the study.
4. The patient has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
5. The patient undergoes rescue keratoplasty (Section5.8.2).
6. Other reasons (eg, pregnancy, development of contraindications of use of study drug).

A patient may be withdrawn from the study for any of the following reasons:

1. The patient withdraws consent.
2. The patient is lost to follow-up.

The investigator will also withdraw all patients if Kowa Research Institute, Inc. terminates the study. The study may be terminated if it becomes apparent that the objectives of the trial cannot be met, or if the frequency or pattern of AEs reported in the trial indicate that the drug is no longer likely to have a positive benefit-to-risk ratio.

4.2.2 Handling of Withdrawals

Patients who withdraw from the study or who are withdrawn from the study will no longer receive study drug. When a patient withdraws or is withdrawn from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who withdraw from the study early will undergo all EOS assessments. Patients who fail to return for final assessments will be contacted by the site with 2 documented telephone calls followed by 1 registered letter, as needed, to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.2.3 Replacements

Patients who are screened for the study and receive a study descemetorhexis may be replaced if they never are randomly assigned study drug or are withdrawn from the study before they administer any study drug. The replacement patients will receive a new randomly assigned treatment and not the treatment assignment of the replaced patient. Patients who self-administer any study drug and subsequently are withdrawn early from the study will not be replaced. Patients who fail to satisfy inclusion and exclusion criteria at screening may be rescreened 1 additional time at the discretion of the sponsor. A special case and conditions for replacement, in case the descemetorhexis fails on the first-selected study eye, is presented in Section 5.8.3.1.

5 Study Drug Treatments

5.1 Method of Assigning Patients to Treatment Groups

After confirmation that the study eye descemetorhexis satisfied inclusion criterion 5 (Section 4.1.1) and any pregnancy test is negative (exclusion criterion 1, Section 4.1.2), patients will be randomly assigned at Visit 2 to either placebo, K-321 BID, or K-321 QID treatment (Section 5.2) using a 1:1:1 allocation ratio. An interactive web response system (IWRS) will be used to administer the randomisation schedule. An independent [redacted] biostatistician will generate the randomisation schedules using SAS software Version 9.4 (SAS Institute Inc, Cary, North Carolina) or later. The IWRS will link sequential patient randomisation numbers to treatment codes. The randomisation schedule will use an appropriate block size, which will not be revealed other than to the [redacted] and Kowa biostatisticians.

5.2 Treatments Administered

There are 3 treatment groups: K-321 ophthalmic solution 0.4% dosed QID (K-321 QID), K-321 ophthalmic solution 0.4% dosed BID (K-321 BID); and placebo. To preserve masking, all patients will self-administer assigned study drug QID and will dose from [redacted] one to be used M/N and the other to be used MD/E, as presented in Table 5-1.

Table 5-1 Vial Contents by Dosing Regimen and Dosing Time for Each Treatment Group From Day 1 to Visit 9 (Week 12)

Treatment	Morning	Mid-day	Evening	Night
K-321 QID	K-321 0.4%	K-321 0.4%	K-321 0.4%	K-321 0.4%
K-321 BID	K-321 0.4%	Placebo	Placebo	K-321 0.4%
Placebo	Placebo	Placebo	Placebo	Placebo

Except on days of study visits on Day 1 through Week 12 (not including Visit 9) during the treatment period, study drug will be dosed by the patient QID: morning (9 AM ±1 hour), mid-day (1 PM ±1 hour), evening (5 PM ±1 hour), and night (9 PM ±1 hour). Each patient will be provided with 2 sets of colour-coded [redacted] one set to be applied M/N and the other to be applied MD/E. See Section 5.4.1 for a detailed description of packaging.

On study visit days Visit 3 through Visit 9, patients will not apply any study drug until after all study measurements have been completed; thereafter on those days, patients will start dosing with the dose closest in timing to the dosing regimen and continue with the remaining doses for the day. Additionally, on Visit 3 they must first apply study drug within [redacted] after the end of the descemetorhexis procedure on Day –1 (Visit 2).

With the primary efficacy endpoint being assessed at Visit 9 (Week 12), if a patient applies any study drug on the day of Visit 9 before all study measurements have been completed, that patient's Visit 9 should be rescheduled within the visit window allowance (eg, the next day). For visits other than Visit 9 during the treatment period, a patient who applies study drug before all study measurements have been completed will be assessed as planned, and a protocol deviation must be recorded.

At Visit 9 (Week 12), patients will enter the drug-tapering phase of the follow-up period, and new study drug will be dispensed without M/N or MD/E colour coding (Section 5.2). All patients will self-administer their tapering-phase study drug BID (9 AM ±1 hour and 9 PM ± 1 hour) for a week, then once daily (9 AM ± 1 hour) for a week, and then will discontinue study drug. At Visit 9, patients will apply the first dose of study drug [redacted] of completing study measurements and will apply the second dose at night, as scheduled. However, if the first dose will be applied after 8 PM, the second dose must be skipped.

For each dose, patients must instil 1 drop to the study eye only and then close the eyelids, pressing on the lacrimal punctum. Patients will be advised to keep the eye closed for 1 to 5 minutes before opening the eye. Any other concurrent ocular medication(s) must be applied at least 5 minutes following instillation of study drug. Patients will be trained by site staff on the application of eye drops.

5.3 Identity of Study Drug

The K-321 ophthalmic solution contains ripasudil 0.4% (4.896 mg/mL of ripasudil hydrochloride hydrate, equivalent to 4.0 mg/mL as the free base) in a solution also containing the excipients sodium dihydrogen phosphate and sodium hydroxide at a pH in the range of 5.0 to 7.0. The solution is isosmotic to normal saline, clear, colourless, and [redacted] The placebo ophthalmic solution is identical in appearance, osmolarity, and pH to the K-321

ophthalmic solution except it does not include ripasudil. [redacted]

The following drug supplies will be used in the study:

Product	Supplied As	Strength
K-321	ophthalmic solution	0.4%
Placebo (vehicle)	ophthalmic solution	0%

[redacted] will manufacture study drug.

5.4 Management of Clinical Supplies

The sponsor will supply sufficient study drug to study sites.

5.4.1 Study Drug Packaging and Storage

Study drug will be prepared in boxed kits [redacted] and shipped by Catalent UK Packaging Ltd. Each pack will contain randomly assigned dosing for 1 patient and will contain a more than sufficient quantity for dispensing during the double-masked treatment period (Table 6-1).

Study drug must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at controlled room temperature [redacted].

[redacted] will be filling [redacted] with study drug. The [redacted] will [redacted] for clinical use at Catalent UK Packaging Ltd. (Westhoughton, Bolton, Lancashire, UK). Study drug is packaged [redacted] being M/N doses, MD/E doses, or tapering-phase doses). The different [redacted] and [redacted] will have different coloured labels. [redacted] Kit labels provide the following information: protocol number., kit number., lot number, patient identification number, study site, investigator, dosing directions, storage requirements, cautionary statements, and country-specific clinical labelling content requirements. Study drug will be dispensed to

selected clinical supply depots where shipments to clinical sites are managed via the IWRS system.

The materials schedule will be prepared by an independent [redacted] biostatistician and provided to the IWRS and the packaging vendor. At the time of randomisation, the IWRS will assign each patient a study drug kit corresponding to the patient's randomly assigned treatment based on the drug supply inventory that is available at the site. The kit will be identified by a unique kit number that is separate from the patient or randomisation numbers. The IWRS will administer study drug dispensing at each visit indicated in Table 6-1.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled, shipped from study sites to Catalent depots in the United States and Germany, and destroyed according to applicable regulations.

5.5 Medication Errors

At Visit 3, patients will be given instructions on how to administer their assigned ophthalmic solution and how to avoid contaminating the [redacted] solution, and they will be observed instilling their own drops by the site staff. Re-education on the proper administration procedure will be given to patients by study site staff throughout the treatment period at each visit. To minimise medication errors during the 12-week treatment phase, [redacted] and [redacted] will be colour-coded differently for M/N and MD/E doses.

5.5.1 Treatment of Medication Errors

In the event of a medication error, the appropriate supportive clinical care must be provided as dictated by the patient's clinical status.

5.5.2 Overdose Management

A symptomatic overdose from topical administration is unlikely, as no overdose was observed during the development of Glanatec (Kowa Company Ltd 2019). Patients will be

instructed to contact the investigator or study coordinator immediately in the event of a suspected symptomatic overdose. Suspected symptomatic overdoses must be reported as AEs (or SAEs) in the eCRF. In the event of overdose, the appropriate supportive clinical care must be provided as dictated by the patient's clinical status

5.5.3 Missed Doses

If a dose is missed, patients will be advised as follows:

- If you notice you missed a dose 2 hours or less after a scheduled dose time, dose immediately

- If you notice you missed a dose more than 2 hours after a scheduled dose time, skip the dose you missed and resume regular dosing at the next planned time according to the schedule. A missed night dose may be taken at any time until midnight of the same day.

5.6 Masking

Study drug will be double-masked. All study drug will be supplied in identical packaging, colour, smell, and appearance to enable double-masked conditions. K-321 and matching placebo will be provided in identical packaging so that all investigators, study site staff, patients, and clinical monitors will remain masked throughout the study. The IWRS will assign study drug to patients at the time of randomisation. Only personnel in IWRS, the independent randomisation team within [redacted] Biostatistics, and clinical supplies will be unmasked and will have access to treatment assignments; all other parties involved in the study will be fully masked.

5.6.1 Unmasking Treatment

A patient's treatment assignment will not be unmasked for the investigator or study site staff until the EOS unless medical treatment of the patient depends on knowing the study treatment the patient received. In the rare event that unmasking is needed because of a medical emergency, the investigator may unmask an individual patient through the IWRS. Reasons for treatment unmasking must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented.

Patients who are unmasked will be allowed to continue their participation in the study; however, their data may be excluded from per-protocol analyses.

5.7 Treatment Compliance

Patient compliance will be determined from [redacted] according to the SOA (Table 6-1). The M/N and MD/E [redacted] will [redacted] separately. The calculations for determining percentage compliance is presented in Section 7.7.5.2.

At each visit during the treatment period, study site staff will remind the patient of the need to administer the ophthalmic drops as instructed.

Before each visit (Visit 4 through Visit 10), study site staff will call patients to remind them to bring all study drug [redacted] to the study site for their visit.

5.8 Prior and Concomitant Therapy

At screening, the following prior therapies will be recorded in the eCRF:

- History of prior study eye surgical procedures
- All medications used within the previous 30 days
- All surgical procedures within the previous 30 days (any body part)

At screening, all patients' prior medications used and surgical procedures undergone within the previous 30 days will be recorded in the eCRF. A history of all prior study eye surgeries must be obtained and recorded (note exclusion criteria 3 and 4, Section 4.1.2).

Use of all concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

All patients' surgical procedures undergone concomitantly during the study must be reported and recorded in the eCRF.

Any concomitant medication or surgical procedure deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication and surgical treatment are recorded in full in the eCRF.

5.8.1 Descemetorhexis of the Study Eye

As a condition of participating in the study, each patient will undergo descemetorhexis of the investigator-selected study eye at Visit 2 (Day –1). See Section 6.1.2 for details.

Recommended post-descemetorhexis concomitant therapy consists [redacted] instilled [redacted] and [redacted] instilled [redacted]. However, an investigator will be able to add [redacted] dosing after [redacted] if the investigator judges it necessary. When more than 1 different eye drop is administered (including study drug), the study drug must be administered first, followed by any non-study eye drop(s) after at least 5 minutes have passed (Section 5.2).

A patient must not be randomly assigned to study drug unless the excised diameter satisfies inclusion criterion 5 (Section 4.1.1).

5.8.2 Rescue Surgical Procedures

Penetrating keratoplasty or endothelial keratoplasty may be offered as rescue surgical procedures to an enrolled patient if the investigator judges that endothelial healing is not complete at Week 12 (Visit 9), or earlier if the investigator considers that the patient needs urgent treatment. If the rescue surgery is performed, the dosing with study drug must be discontinued immediately (without tapering) and the patient will attend all planned study visits including the follow-up period.

5.8.3 Prohibited and Restricted Concomitant Therapy

5.8.3.1 Prohibited and Restricted Surgical Intervention

Throughout the study, study eyes must not undergo any surgical intervention other than the descemetorhexis at Visit 2. Non-study eyes must not undergo any surgical treatment for FECD or cataract in the screening or treatment periods, but they can be surgically treated

during the follow-up period. The non-study eye will not be eligible for participation in the trial, except if the descemetorhexis fails on the first-selected study eye and that eye is not eligible to participate. In that case, if all other inclusion and exclusion criteria are met by the second eye and more than 30 days have passed since the first study descemetorhexis, then the patient can be enrolled using the second eye to qualify.

Punctal occlusion plugs are considered to be surgical interventions.

5.8.3.2 Prohibited and Restricted Medication

The following medications and drugs identified as exclusion criteria are prohibited for use by patients throughout the study:

- Netarsudil or other ROCK inhibitors
- Eye drops and ointments containing 5% sodium chloride
- Devices to improve any ocular symptoms (eg, TrueTear®, LipiFlow®, etc)
- Drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates, or benzodiazepines) or more than 2 standard drinks of alcohol per day
- Contact lenses (except non-study eye)
- Any ophthalmic solution besides artificial tears, over-the-counter anti-allergic ophthalmic products, study drug, or drugs prescribed by the investigator for treatment of the underlying condition
- Any investigational drug besides study drug

6 Study Assessments and Procedures

Before performing any study procedures, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

The SOA is presented in Table 6-1. Detailed instructions for study site activities will be provided in the study manual.

Table 6-1 Schedule of Study Site Activities

Activity	Screening	Treatment Period									Follow-Up Period				
Time Point	Day -28	Day –1	Day 1	Week 1	Week2	Week 3	Week 5	Week 7	Week 9	Week 12	Week 16	Week 20	Week 24	Week 38	Week 52
Visit Window (Day)	-28 to -7	-	-	5-9	12-16	18-24	32-38	46-52	60-66	81-87	105-119	133-147	161-175	259-273	357-371
Visit No.	Visit 1	Visit 2	Visit 3	Visit 4	Optional Visit	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Informed consent	X														
Demographics	X														
Medical history and concomitant disease	X	X [a]													
Physical examination and vital sign measurements	X														
Urine drug screen	X														
Urine pregnancy test (if applicable)		X [a]									X				
Laboratory sampling	X									X					
Eligibility evaluation	X	X [b]													
Descemetorhexis with photo or video documentation		X													
Randomisation		X													
Dispense study drug			X	X		X	X	X	X	X					
[redacted] study drug [c]				X	(X) [d]	X	X	X	X	X	X				
Study drug administration			X	X	(X) [d]	X	X	X	X	X					
Slit-lamp evaluation	X	X [a]	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal ECD measurement [e] (specular microscopy, non-contact type)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal ECD measurement by HRT [f]	(X)			(X)	(X) [d]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

Activity	Screening	Treatment Period									Follow-Up Period				
Time Point	Day -28	Day –1	Day 1	Week 1	Week2	Week 3	Week 5	Week 7	Week 9	Week 12	Week 16	Week 20	Week 24	Week 38	Week 52
Visit Window (Day)	-28 to -7	-	-	5-9	12-16	18-24	32-38	46-52	60-66	81-87	105-119	133-147	161-175	259-273	357-371
Visit No.	Visit 1	Visit 2	Visit 3	Visit 4	Optional Visit	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
BCVA (ETDRS scale)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal thickness (ultrasound pachymeters)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Corneal morphology (Pentacam or Orbscan)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity [f] (CSV-1000 chart)	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Intra-ocular pressure (contact or non-contact type tonometer)	X		(X) [g]	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
[redacted]	X						X			X			X		X
Photo documentation of ocular findings	X			X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X
Adverse event documentation		X	X	X	(X) [d]	X	X	X	X	X	X	X	X	X	X

Abbreviation: HRT, Heidelberg retina tomography; [redacted]

[a] Pre-operative.

[b] Post-operative.

[c] Both [redacted] study drug [redacted] will [redacted] and [redacted] will be recorded in the eCRF. Morning/night and mid-day/evening drug will [redacted] separately. At the optional Week 2 visit, a patient's study drug will [redacted] returned to the patient. At Visit 10, study drug [redacted] from the drug tapering phase (Week 12 through Week 14) will [redacted].

[d] Week 2 is an optional visit (at the discretion of the investigator), but if this visit is applied, all marked assessment items must be conducted.

[e] The study eye must be measured at all indicated visits, whereas the non-study eye must be measured only at Visit 1 and Visit 14.

[f] Only at sites where equipment is available.

[g] If investigator judges it necessary.

6.1 Eligibility Assessments and Procedures

6.1.1 Medical History, Physical Examination, and Laboratory Assessments

Medical history and assessments of concomitant disease, physical examination and vital sign measurements, urine screening for drugs of abuse, pregnancy screening for patients of childbearing potential, and clinical laboratory assessments will be conducted at screening primarily to assess eligibility to participate in the study. The limited physical examination includes a review of the patient's medical and medication history and subsequent evaluation of relevant body system complaints. In case of relevant findings, full evaluation of the condition needs to be conducted. Demographics information will be collected at screening as follows: age, race, iris colour, and sex.

6.1.2 Descemetorhexis of the Study Eye

Each patient will undergo descemetorhexis of the investigator-selected study eye at Visit 2 (Day –1). A digital photo of the study eye must be taken immediately before and immediately after descemetorhexis at Visit 2. The investigator will perform descemetorhexis to remove central confluent guttae, removing an area of Descemet membrane with a diameter of [redacted] The longest diameter and the shortest diameter must be recorded in the eCRF. The procedure must be recorded by video to record potential differences in technique among investigators. Also, immediately after the operation, the stripped area will be recorded by photo or video with an adjacent scale to measure the area removed. Detailed guidance for performing the study eye descemetorhexis will be provided in the study manual.

Recommended post-descemetorhexis concomitant therapy is described in Section 5.8.1.

6.2 Efficacy Assessments

6.2.1 Corneal Endothelial Cell Density Measurement

6.2.1.1 Non-Contact Specular Microscopy

Corneal ECD will be measured by non-contact specular microscopy. The study eye must be assessed at all study visits as indicated in Table 6-1, whereas the non-study eye must be measured only at Visit 1 and Visit 14. The same instrument must be used for all study visits for a given patient throughout the study. All specular microscope images taken will be sent to

the [redacted] for analysis via a designated portal site. Please see the study manual for detailed instructions.

6.2.1.2 Heidelberg Retina Tomography

Heidelberg retina tomography (HRT) of the study eye will be performed according to the schedule in Table 6-1 if the necessary equipment is available at the study site before the start of the study at that site. All HRT images taken will be sent to the [redacted] for analysis via a designated portal site. Please see the study manual for detailed instructions.

6.2.2 Corneal Thickness

Corneal thickness of the study eye will be measured by contact ultrasound pachymetry on the central cornea. The same instrument must be used for all study visits for a given patient throughout the study. From a safety perspective, the corneal thickness of both eyes must be measured, and the results must be recorded. See the study manual for detailed instructions.

6.2.3 Corneal Oedema

Corneal oedema of the study eye will be categorised by epithelial, stromal, or endothelial, and assessed by the investigator as either present or absent.

6.2.4 Corneal Morphology

Corneal morphology of the study eye will be assessed by OCULUS Pentacam® or Bausch and Lomb Orbscan®. If the site has both instruments, the OCULUS Pentacam will be used. The same instrument must be used for all study visits for a given patient throughout the study. All data and images must be recorded.

6.2.5 Best Corrected Visual Acuity

The BCVA of the study eye will be assessed by ETDRS testing without pupil dilation. For all measurements, the BCVA letter score will be recorded. Please see the study manual for detailed instructions on the BCVA ETDRS assessment.

6.2.6 Contrast Sensitivity

Visual contrast sensitivity of the study eye will be assessed using the VectorVision CSV-1000 instrument if the necessary equipment is available at the study site before the start of the

study at that site. Please see the study manual for detailed instructions on the CSV-1000 assessment.

6.2.7 [redacted]

[redacted]

6.3 Safety Assessments

6.3.1 Ocular Safety Assessments

All ocular safety assessments must be performed on both eyes of each patient. Refer to the study manual for detailed instructions on each of the ocular safety assessments to be performed in this study.

The examiners must use the same mode of measurement throughout the entire study for a given patient, and the assessments must be performed by the same evaluator for a given patient.

Slit-lamp biomicroscopy will be performed at every visit using slit-lamp examination without pupil dilation to evaluate the condition of the lids, conjunctiva, anterior chamber, cornea, and lens. Additionally, digital photographs of the study eye will be taken during the slit-lamp procedure according to the study manual description. The images will be provided to the sponsor for review.

Intra-ocular pressure (IOP) may be measured by either contact or non-contact tonometry, but the same method must be used for all study visits for a given patient throughout the study and all reasonable efforts must be made to have the same examiner obtain all IOP measurements for a given subject. At each study visit, a single IOP measurement will be made for each eye, with pressure recorded in millimetres of mercury (mm Hg). The IOP measurement is at the investigator's discretion at Day 1 (Visit 3).

Ocular examination will be performed with pupil dilation using an indirect ophthalmoscope according to the current standard of practice to evaluate the condition of the vitreous, macula, retina, optic nerve, choroid, and retinal [redacted]

6.3.2 Adverse Events

6.3.2.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Patients will be instructed to contact the investigator at any time after randomisation if any symptoms develop.

An AE may include the following:

- Exacerbation of a pre-existing disease or symptom
- Increase in frequency or intensity of a pre-existing event or condition
- A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study

An AE does not include the following:

- Medical or surgical procedures (although the condition that leads to the procedure must be reported as an AE)
- Pre-planned medical procedures (eg, planned surgical interventions, investigations, social and/or convenience hospitalisations)
- Pre-existing disease or conditions present at the time of signing the ICF are considered concurrent medical conditions and must not be recorded as an AE

The investigator must attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis must be documented as the AE and not as the individual signs or symptoms.

The investigator will evaluate any changes in laboratory values and other study investigations and determine whether the change is clinically important and whether it is related to the study drug. The investigator must record the AE or investigation abnormality in the eCRF regardless of the relationship to the study drug (ie, the AE will be recorded whether or not it is considered related to the study drug).

The criteria for determining whether an abnormal objective test finding must be reported as an AE are as follows:

- The test result is associated with accompanying symptoms
- The test result requires additional diagnostic testing or medical/surgical intervention
- The test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy and/or
- The test result leads to any of the outcomes included in the definition of an SAE

Merely repeating an abnormal test, in the absence of any of the above conditions, does not require reporting as an AE. An abnormal test result that is determined to be an error or artefact does not require reporting as an AE.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that

- results in death.
  Any death resulting from an AE occurring during the study period or within 30 days after the last dose of the study drug, even if the death appears to be completely unrelated to the study or study drug.
- is immediately life threatening.
  The term ‘life-threatening’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation.
  The term ‘hospitalisation’ means a hospital admission or an overnight stay; prolongation means delay of a planned or anticipated discharge date by at least 1 overnight stay.
  Adverse events which require attendance at hospital but do not require admission may be considered medically important.
- results in persistent or significant disability/incapacity.
- results in impairment, damage, or disruption in the study patient’s body function or structure, or physical ability or quality of life.
- is a congenital anomaly/birth defect.
  Additionally, events in which there is suspicion that exposure of either parent to the study drug resulted in an adverse outcome in the offspring is a medically important event.
- Is medically important: an event that may not be immediately life-threatening or fatal or result in hospitalisation, but may require intervention to prevent one of the serious outcomes listed above.
  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

6.3.2.2 Eliciting and Documenting Adverse Events

The investigator is responsible for reporting AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. Serious AEs will be collected from the time that the patient gives consent to participate in the study until 30 days after the date of last dosing or of completion or withdrawal from the study, whichever is latest. All AEs will be collected starting from the time that the patient gives consent until the date of completion or withdrawal from the study.

Serious AEs that occur more than 30 days after the last dose of study drug or after exit from the study, whichever is later, need not be reported unless the investigator considers them related to study drug.

At each study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been

hospitalised, had any accidents, had any eye surgery, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (eg, laboratory values, physical examination findings) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF.

6.3.2.3 Reporting Adverse Events

All AEs reported or observed will be recorded on the AE page of the eCRF. Information to be collected includes event term, time of onset, date of resolution of the event, seriousness, severity, relatedness to study drug, any required treatment or evaluations, and outcome.

The investigator will assess the severity of the event. The severity (intensity) of AEs must be classified using the following criteria:

- **Mild**: An AE that is easily tolerated by the patient, causes minimal discomfort, and does not interfere with everyday activities
- **Moderate**: An AE that causes enough discomfort to interfere with normal everyday activities and may require intervention
- **Severe**: An AE that prevents normal everyday activities (treatment or intervention will usually be required). Severe events are usually incapacitating

When changes in the severity of an AE occur more frequently than once a day, the maximum intensity for the event must be noted for that day. Any changes in intensity of signs and symptoms over multiple days will be captured by recording new AEs, with the amended intensity grades and the dates (and time, if known) of the change(s). Changes in the intensity of an AE must be documented to allow an assessment of the duration of the event at each level of intensity.

The investigator will assess the causal relationship between the study medication and the AE and decide whether, in his or her qualified medical judgement, there is a reasonable possibility that the event may have been caused by the study drug. There are 2 categories of causality:

- **Unrelated**: If no valid reason exists for suggesting a relationship, or the event may plausibly be related to the patient's clinical condition, an underlying disease or other medication taken by the patient, then the AE must be considered unrelated.

- **Related**: If there is any valid reason for supposing that there is a relationship between the study medicine and the AE, especially if the even improves on withdrawal of the drug (de-challenge) or recurs on recommencement of therapy (re-challenge), then the AE must be considered related. The AE must not be considered related simply because it is not possible to rule out an association between the AE and the study drug.

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event must be reported.

The action taken with the study medication must be recorded as treatment continued, treatment interrupted, or treatment discontinued. If the patient is no longer taking study medication at the time of the event, then action taken must be recorded as not applicable.

All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any AE that meets SAE criteria (Section 6.3.2.1) must be reported to the [redacted] Pharmacovigilance Department immediately (ie, within 24 hours) after the time site staff first learn about the event, using the electronic data capture (EDC) system. If for any reason the EDC is not available to the study site, the following contact information is to be used for SAE reporting:

[redacted] **Pharmacovigilance Department**
[redacted]
[redacted]

If the initial contact to [redacted] Pharmacovigilance is made via the SAE Hotline or the SAE fax line, the SAE must still be reported, urgently, using the EDC system when it becomes available. Details on SAE reporting are presented in the study manual.

6.3.2.4 Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SUSAR cases, the sponsor will assess the expectedness of these events using the Reference Safety Information section of the study drug investigator's brochure.

The sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

6.3.2.5 Follow-Up of Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to resolution, until the investigator deems the event to be chronic or not clinically significant (NCS), or until the patient is considered stable. Adverse events that are ongoing at the time of the EOS visit are to be followed for 30 days or until resolution, until the investigator deems the no longer clinically significant (CS), or until the investigator considers the patient’s condition stable.

6.3.3 Vital Sign Measurements

The following vital signs will be measured:

- Blood pressure (measured supine, systolic and diastolic [mm Hg])
- Pulse (beats per minute)
- Body temperature (°F)
- Height (cm) and body weight (kg). Height is to be measured at screening only.

Supine blood pressure, pulse, and body temperature (°F) will be recorded after the patient has been recumbent and at rest for at least 5 minutes.

6.3.4 Eligibility

Eligibility will be evaluated at screening (Visit 1) and post-operatively on Day –1 (Visit 2). Patients must meet all inclusion criterion and no exclusion criteria to be assigned study drug.

6.4 Safety Monitoring Committee

There will be no safety monitoring committee.

6.5 Pregnancy

Female patients of childbearing potential (defined in inclusion criterion 5 of Section 4.1.1) are required to use effective contraception throughout the study.

Acceptable methods of contraception for female patients include oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted/injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides). Note: female patients who are actively practising abstinence or who have a partner that is sterile (eg, vasectomy) will be permitted to participate in the study without contraception use.

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure patient safety, each pregnancy must be reported to [redacted] sponsor within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages and congenital abnormalities of the child must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after study completion, and considered by the investigator as possibly related to the study treatment, must be promptly reported to [redacted] sponsor.

6.6 Laboratory Analyses

Routine laboratory analyses will be performed by a central laboratory and will include the following assessments:

- **Haematology**: haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and absolute platelet count.
- **Clinical chemistry**: total protein, sodium, potassium, chloride, albumin, glucose, HbA1c, blood urea nitrogen, creatinine, bilirubin (total and direct), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, lactate dehydrogenase.
- **Urinalysis**: pH, glucose, ketones, specific gravity, nitrite, protein, bilirubin, urobilinogen, and blood. Microscopic urinalysis will be performed if urinalysis results are abnormal.

Urine pregnancy testing will be performed for all patients of childbearing potential before descemetorhexis at Visit 2 and at Visit 10.

Urine screening for drugs of abuse (opiates, methadone, cocaine, amphetamines, barbiturates benzodiazepines) and alcohol will be performed by dipstick.

6.6.1 Future Genetic Testing

A 6-mL blood sample will be obtained at Visit 1 for archiving and future genetic testing (Section 2.3). The blood sample will be collected only at sites in countries where allowed by local regulations and where approved by the IRB/IEC and relevant regulatory authorities.

Results of genetic testing will not be reported to the patient, relatives, or attending physician, and they will not be recorded in the participant's medical record. The participant may withdraw consent for genetic testing at any time up to analysis, even after the samples have been obtained. In the event of withdrawal of consent, the bio-repository will be notified to pull and destroy the sample.

For all samples collected for genetic testing, precautions are to be taken to maintain confidentiality by de-identifying the sample to prevent the genetic data from being linked to the identity of the participant.

6.7 Sample Collections

Sample collection, processing, and shipping must be performed according to local laboratory requirements and consistent with detailed procedures described in the study manual.

The volume of blood sampled is planned to be less than 20 mL in a single day and less than 35 mL over the entire study.

7 Statistical and Analytical Plan

A study eye will be identified for each patient. Unless otherwise specified, efficacy will be summarised for the study eye only. Ocular safety summaries by eye will be presented separately for the study eye and the non-study eye. Baseline measurements are the last measurements taken during the screening period (before Visit 2).

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the central corneal ECD at Week 12 as assessed by the [redacted]

7.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Central corneal thickness change from baseline to each subsequent visit
- Percent change of central corneal thickness from baseline to each subsequent visit
- Central corneal ECD at each visit
- Number and percentage of patients who achieve central corneal ECD of 700 cells/mm^2 or more at each visit
- Time to achieve central corneal ECD 700 cells/mm^2 or more
- Number and percentage of patients who achieve cornea clearance at each visit where corneal clearance is defined as patients achieving a cornea thickness less than or equal to baseline cornea thickness and who have no corneal oedema
    - Number and percentage of patients who achieve cornea thickness less than or equal to baseline cornea thickness
    - Number and percentage of patients who achieve no corneal oedema
- Time to cornea clearance

- Time to return of cornea thickness to less than or equal to baseline cornea thickness
- Time to no corneal oedema

7.3 Exploratory Endpoints

Exploratory endpoints include the following:

- BCVA (letters) by ETDRS change from [redacted] to [redacted]
- Time to achieve BCVA by ETDRS letter score [redacted]
- Number and percentage of patients who achieve [redacted] or more improvement (BCVA by ETDRS)
- [redacted] corneal ECD at [redacted]
- [redacted] corneal ECD change from [redacted] at [redacted]
- Percent change of [redacted] corneal ECD from [redacted] at [redacted]
- Changes in [redacted] parameters from [redacted]
- Contrast sensitivity change (log values) from [redacted]
- [redacted] domain and total scores change from [redacted]

7.4 Sample Size Calculations

A sample size of 20 patients in each group will be needed to detect a difference of [redacted] in the measurement in the corneal ECD at Week 12 between K-321 0.4% QID/BID and placebo groups with a power of [redacted] for Step 1 and a power of [redacted] for Step 2 using a Wilcoxon rank sum test with a 0.050 two-sided significance level with closed testing procedures. Sample size was calculated by simulation. For the simulation, based on the existing literature, placebo was assumed to be distributed normally with [redacted] and K-321 was assumed to be distributed normally with [redacted]

[redacted] Proportion of unmeasurable value of Week 12 due to corneal oedema and proportion of [redacted] value of Week 12 due to the withdrawal were assumed to be about 10% and about 5%, respectively.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full-analysis set (FAS): The FAS will consist of all participants who have a successful descemetorhexis procedure performed, were randomly assigned to receive double-mask study drug, received at least one dose of study drug in the study eye, and have at least one assessment of central corneal ECD performed after the descemetorhexis procedure on the study eye. (An assessment of "cannot perform due to corneal oedema" is considered a valid assessment for inclusion in the FAS.) All analyses using the FAS will group participants according to randomised treatment.

Per-protocol set (PPS): The PPS will consist of all FAS participants who complete the 12-week dosing treatment period for the study eye (for the primary analysis only), have at least 80% compliance with study treatment for the study eye, have not taken any prohibited medication, and have no major protocol deviations. Patients who receive rescue therapy will be considered to have completed study treatment for inclusion in the PPS. All analyses using the PPS will group participants according to treatment actually received.

Safety set (SFS): The safety set will consist of all participants who received any study drug. All analyses using the safety set will group participants according to treatment actually received.

The FAS will be the primary analysis set for efficacy analyses. Selected efficacy analyses will be repeated for the PPS. Safety will be summarised using the SFS.

7.6 Description of Subgroups to be Analysed

Due to the small sample size, no subgroup analyses are planned.

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarised using the mean, the SD, median, minimum value, and

maximum value. Categorical variables will be summarised using frequency counts and percentages. Unless otherwise noted, the denominator to determine the percentage of participants in each category will be based on the number of participants with available data. Selected ordinal data may be summarised using both descriptive statistics and counts and percentages of participants in each category, as appropriate. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan (SAP).

All statistical tests will be 2-sided and performed using a 0.05 significance level, leading to 95% (2-sided) CIs.

A closed 2-step ordered testing procedure will be used to control overall type I error for the primary efficacy endpoint, central corneal ECD at Week 12. In step 1, the K-321 0.4% QID group will be statistically compared with the placebo group. If the step 1 comparison is significant, step 2 will be performed to statistically compare K-321 0.4% BID group with the placebo group. If the statistical comparison made during step 1 is not significant, testing will still be performed to compare the BID group to placebo; however, all p values will be considered nominal/descriptive only.

No other measures will be taken to control error for the multiple secondary and exploratory endpoints or multiple treatment comparisons.

7.7.1 Analysis of Primary Efficacy Endpoint

The primary analysis of central corneal ECD will be performed on the study eye within the FAS via a Wilcoxon rank sum test and will be based on assessments performed by specular microscopy. Testing will be performed in a pairwise manner with each dosing regimen (QID and BID) of K-321 0.4% compared to placebo. For each dosing regimen, the following 2-sided hypothesis will be tested

$$H_o: \Delta = 0 \text{ versus } H_a: \Delta \neq 0$$

where Δ is the shift in location in central corneal ECDs between the active and placebo groups being compared: ie,

$X_i = e_i$ for i = 1 to n for the placebo patients

$Y_j = e_j + \Delta$ for j = 1 to m for the K-321 patients

The Hodges-Lehmann estimate (Hodges and Lehmann 1963) for the shift in location (eg, the median of all differences $d=Y_j - X_i$) and Moses 95% CI (Moses 1965) will also be presented.

Week 12 assessments that are unable to be performed due to corneal oedema will be [redacted] Week 12 assessments that are [redacted] due to patient withdrawal or missed visit will be [redacted] Patients who receive a rescue keratoplasty performed prior to Week 12 will be [redacted]

Sensitivity analyses will be performed by repeating the above analysis and [redacted] for the PPS. The primary analysis methods will also be repeated for the FAS using [redacted] Additionally, analyses will be performed using assessments performed by HRT for the subset of patients for which the assessments are available.

7.7.2 Analysis of Secondary Efficacy Endpoints

Secondary endpoints will be summarised for the FAS. Central ECD which cannot be performed due to corneal oedema will be [redacted] for analysis. Assessments of central ECD, central corneal thickness, and epithelial oedema after rescue keratoplasty will be [redacted] Otherwise, secondary efficacy analyses will be [redacted]

Endpoints based on continuous measures (central ECD at each visit, central corneal thickness change from baseline to each visit, and percent change of central corneal thickness from baseline to each visit) will be analysed by pairwise Wilcoxon rank sum tests comparing each

active K-321 0.4% treatment. The Hodges-Lehmann estimate and Moses 95% CI for the shift in location will also be presented regimen to placebo.

Endpoints based on the number and percentage of patients achieving the endpoint (patients who achieve central ECD of 700 cells/mm^2 or more, patients who achieve cornea clearance at each visit, patients who achieve a cornea thickness less than or equal to baseline cornea thickness at each visit, and patients who have no corneal oedema at each visit) will be analysed by pairwise Fisher's Exact or Pearson chi-square tests comparing each active K-321 0.4% treatment regimen to placebo. The 95% CI for the difference in percentage of patients achieving the endpoint will also be presented.

Endpoints based on time-to-event endpoints (time to achieve central ECD 700 cells/mm2 or more, time to cornea clearance, time to return of cornea thickness to less than or equal to baseline cornea thickness, time to no corneal oedema) will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo. Kaplan-Meier estimates and plots will also be presented. Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be [redacted] Patients who receive rescue keratoplasty will be [redacted]

7.7.3 Analyses of Exploratory Efficacy Endpoints

Exploratory endpoints will be summarised for the FAS. Assessments after rescue keratoplasty will be [redacted] Endpoints will be analysed in a similar manner to the secondary efficacy endpoints.

Endpoints based on continuous measures will be analysed by pairwise Wilcoxon rank sum tests comparing each active K-321 0.4% treatment regimen to placebo with the Hodges-Lehmann estimate for the different in medians and Moses 95% CI for the difference in medians also presented.

Endpoints based on the number and percentage of patients achieving the endpoint will be analysed by pairwise Pearson chi-square tests comparing each active K-321 0.4% treatment regimen to placebo with the 95% CI for the difference in percentage of patients achieving the endpoint also presented.

Endpoints based on time-to-event endpoints will be analysed by pairwise log-rank tests comparing each active K-321 0.4% treatment regimen to placebo with Kaplan-Meier estimates and plots also presented. Patients who complete follow-up or discontinue the study without achieving the specified endpoint will be [redacted] Patients who receive rescue keratoplasty will be [redacted]

7.7.4 Safety Analyses

Safety parameters include monitoring of AEs, TEAEs, vital sign measurements, laboratory examinations, slit-lamp biomicroscopy, IOP, and ophthalmoscopy.

Safety data will be summarised and listed with no statistical hypothesis testing performed. Continuous variables will be summarised using the mean, the SD, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages.

7.7.4.1 Adverse Events

All AEs will be listed and all TEAEs will be summarised. Adverse events will be deemed treatment-emergent if the onset date is on or after the date of first treatment. Events which are not treatment-emergent will be listed separately and together with all other AEs. AEs will be summarised separately for the treatment period, the tapering phase, and the 9-month follow-up period. Ocular TEAEs will be summarised separately from non-ocular TEAEs. Ocular TEAEs will be summarised separately for the study eye and non-study eye.

Treatment-emergent AEs will be summarised by treatment group, presenting the number and percentage of patients having a TEAE in each system organ class and having each individual TEAE based on the preferred term. Treatment-emergent AEs will also be tabulated according to intensity and causality. Patients who experienced multiple TEAEs for a preferred term will be counted once, similarly for patients with multiple TEAEs per system organ class.

Deaths, SAEs, and TEAEs leading to discontinuation of study treatment will be listed separately and, if appropriate, summarised by treatment group, system organ class and preferred term.

7.7.4.2 Vital Signs

Observed values at each visit and change from baseline values for vital sign measurements will be summarised descriptively by treatment group. All vital sign measurement data will be listed.

7.7.4.3 Clinical Laboratory

Observed values at each visit and change from baseline values for clinical laboratory evaluations will be summarised descriptively by treatment group. Additionally, shift tables will be presented for chemistry and hematology parameters from baseline to each post-baseline assessment. All clinical laboratory data will be listed.

7.7.4.4 Intra-Ocular Pressure

All IOP data will be listed. Observed values at each visit and change from baseline values for IOP evaluations will be summarised descriptively by treatment group for the study eye and non-study eye.

7.7.4.5 Slit-Lamp Biomicroscopy and Ophthalmoscopy

Ocular findings will be evaluated by the following criteria:

- Normal
- Abnormal (NCS)
- Abnormal with clinical significance (CS)

Data from all slit-lamp biomicroscopy and ophthalmoscopy assessments will be listed. The number and percentage of patients with at least 1 treatment-emergent CS abnormality by ocular assessment will be summarised for each treatment group for the study eye and non-study eye. An abnormality will be deemed treatment-emergent if the onset date is on or after the date of first treatment. A patient will be counted once even if the patient experiences more than 1 treatment-emergent CS abnormality.

7.7.5 Other Analyses

7.7.5.1 Patient Demographics and Other Baseline Characteristics

Descriptive statistics will be provided by treatment group for patient demographics and all ocular and baseline characteristics. Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by treatment group. Ocular summaries will be presented for the study eye and the non-study eye. Other relevant baseline information will be listed and summarised as appropriate with descriptive statistics. Analyses will be based on the FAS.

7.7.5.2 Treatment Exposure and Compliance

Descriptive statistics will be provided to characterise study treatment exposure and compliance using the safety set. Summaries will also be provided for the FAS if it differs from the safety set. Duration of exposure will be calculated in days as the (date of last dose – date of first dose + 1). Percent compliance will be calculated as the total number of study drug instillations/planned number of instillations × 100. The planed number of instillations for Visit 3 (Day 1) will be adjusted based on the time the descemetorhexis was completed on Visit 2 (Day –1) and the time all study visit assessments are completed on Visit 3. For all other study visits during the treatment period, the planed number of instillations will be adjusted based on the time all planned study visit assessments are completed on the respective study visit days, as activities on these days may reduce the number of doses that can be given. The details of dosing adjustment will be provided in the SAP. For all other study days, the number of planned instillations will be considered to be 4 doses. If the first and last doses are administered on the same day, the number of planned instillations will be based on the time of the first dose. Subjects will be considered compliant with study treatment if the calculated percent compliance is between 80% and 125%, inclusive.

7.7.6 Interim Analyses

No interim analyses will be performed. The primary analysis will be conducted at the Week 12 database lock ie, after all patients have completed dose tapering at the Week 16 visit or have been discontinued from the study and/or treatment before this visit. Analysis of the complete study data (through Week 52) will be performed after all patients have completed

the Week 52 visits or have been discontinued from the study before the Week 52 visit. As the primary efficacy endpoint is at the Week 12 visit, no alpha adjustments will be required. No changes to study conduct (eg, change to sample size or early stopping) are planned.

8 Data Quality Assurance

The sites will maintain source documentation and enter patient data into the eCRF as accurately as possible and will rapidly respond to any reported discrepancies. Electronic CRFs are accessed through Medidata Rave® (Medidata Solutions Inc, New York, New York). This EDC system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11. Each person involved with the study will have an individual user name and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. A quality review of the data will be performed by the site with additional reviews by the clinical monitor through source data verification.

Each eCRF is presented as an electronic copy, allowing data entry by site staff, who can add and edit data, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed by the investigator. This system provides site staff, monitors, and reviewers with access to hard copy audits, discrepancy reviews, and investigator comment information.

After all data reviews and query resolutions are complete, the SAP is approved and signed, and any summary/analysis populations are approved, the database will be locked.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, etc. All eCRF information is to be completed. If an item is not available or is not applicable, this fact must be indicated. Blank spaces must not be present unless otherwise directed.

Investigative site personnel will enter patient data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events and medical history will be coded using the MedDRA terminology. Concomitant medications will be coded using the most current available WHO Drug Dictionary.

After database lock, each study site will receive an electronic copy of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, an electronic copy of all the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate electronic copy for their records. In all cases, patient initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Country regulations, US federal regulations, and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB or IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP) and with applicable regulations in the countries where the study will be conducted will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals must be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favourable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable country and local regulations.

9.3 Patient Information and Consent

A written informed consent in compliance with regulatory authority regulations or US Title 21 CFR Part 50 shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any

institution-specific modifications to study-related procedures are proposed or made by the site, the consent must be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF. The investigator will then sign the consent signed by the patient/legal guardian.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be patient to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA), the Medicines and Healthcare Products Regulatory Agency (MHRA), other agencies, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the patient's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval.
- Original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae (CV) for the investigator and each sub-investigator listed on Form FDA 1572.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all applicable national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines, regulations, and laws, and consistent with the principles of the Declaration of Helsinki.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the contract research organization [redacted] and/or IRB/IEC according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, when applicable, must inform the institution. Also, the investigator/institution must provide the IRB/IEC with a summary of the study's outcome and provide the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents must be retained for at least 25 years. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The patients' medical records, however, need only be retained as long as required by the institution, in accordance with national law.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorisation from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The administrative structure is presented in Table 11-1.

Table 11-1 Study Administration

Role	Name/Affiliation/Address
Sponsor	Kowa Research Institute, Inc. 430 Davis Drive, Suite 200 Morrisville, NC 27560
Sponsor Contact	[redacted]
Contract Research Organisation	
Study Medical Monitor	
Central Laboratory	
[redacted]	

11.1 Monitoring

11.1.1 External Data Monitoring Committee

There will be no external data monitoring committee.

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator must promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee before implementation. Amendments to the protocol must be submitted in writing to the investigator’s IRB/IEC for approval before patients can be enrolled into an amended protocol or before the amendment can be implemented for patients already participating in the study.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments must be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient or to the integrity of the study. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to FDA regulations or ICH GCP guidelines, and will lead either to the patient being discontinued from study drug treatment or withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC must be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Kowa Research Institute, Inc. has every intention of completing the study, Kowa Research Institute, Inc. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes his or her last visit.

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports and the standards of regulatory agencies to which the clinical study reports will be submitted.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

Elhalis H, Azizi B, Jurkunas. UV. Fuchs endothelial corneal dystrophy. Ocul Surf. 2010;8(4):173-84.

Garcerant D, Hirnschall N, Toalster N, et al. Descemet's stripping without endothelial keratoplasty. Curr Opin Ophthalmol. 2019;30(4):275-85.

Hodges JL Jr, Lehmann EL. Estimates of location based on rank test. Ann. Math Statist. 1963;34(2):598-611.

Ianchulev T, Lane S, Masis M, et al. Corneal endothelial cell density and morphology after phacoemulsification in patients with primary open-angle glaucoma and cataracts: 2-year results of a randomised multicenter trial. Cornea. 2019;38(3):325-31.

Jullienne R, Manoli P, Tiffet T, et al. Corneal endothelium self-healing mathematical model after inadvertent descemetorhexis. J Cataract Refract Surg. 2015;41(10):2313–8.

Kowa Company Ltd. Ripasudil hydrochloride hydrate ophthalmic solution. Investigator's Brochure, version 00.01. Tokyo (Japan); 2019. 115 p.

Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119(7):1050-8.

Macsai MS, Shiloach M. Use of topical rho kinase inhibitors in the treatment of Fuchs dystrophy after Descemet stripping only. Cornea. 2019;38(5):529-34.

Moloney G, Petsoglou C, Ball M, et al. Descemetorhexis without grafting for Fuchs endothelial dystrophy-supplementation with topical ripasudil. Cornea. 2017;36(6):642-8.

Moses LE. Query 10: Confidence limits from rank tests. Technometrics. 1965;7(2):257-60.

Van den Bogerd B, Dhubhghaill SN, Koppen C, et al. A review of the evidence for in vivo corneal endothelial regeneration. Surv Ophthalmol. 2018;63(2):149–65.

Watanabe S, Oie Y, Fujimoto H, et al. Relationship between corneal guttae and quality of vision in patients with mild Fuchs' endothelial corneal dystrophy. Ophthalmology. 2015;122(10):2103–9.